White matter lesions are associated with cortical atrophy more than entorhinal and hippocampal atrophy

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Abstract. The goal of this study was to examine the relationship between subcortical vascular disease and brain atrophy in patients with Alzheimer's disease (AD) and mixed dementia (i.e., AD and subcortical vascular disease together). MRI was performed on 77 cognitively normal (CN) subjects, 50 AD and 13 mixed dementia patients. Subcortical vascular disease was determined by white matter hyperintensities (WMH) volume and presence of subcortical lacunes. Brain atrophy was measured using total brain cortical gray matter (CGM), entorhinal cortex (ERC) and hippocampal volumes. CGM volume, but not ERC or hippocampal volume was inversely related to WMH volume in patients and controls. In contrast, no relationship was detected between CGM, ERC, or hippocampal volumes and subcortical lacunes. Furthermore, no interaction was found between WMH and diagnosis on cortical atrophy, implying that WMH affect cortical atrophy indifferently of group. These results suggest that subcortical vascular disease, manifested as WMH, may affect cortical atrophy more than ERC and hippocampal atrophy. Further, AD pathology and

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1. Introduction

Alzheimer's disease (AD) is a major cause of dementia and subcortical vascular disease is often a confounding and complicating factor in the development of dementia [21]. T2-weighted MRI of the brain often shows regions of strong signal intensity in the white matter (WM), called white matter hyperintensities (WMH) in cognitive normal (CN) elderly subjects and patients with AD and a variety of other disorders [2,10,15,21]. WMH have been thought to be incomplete infarcts characterized by partial loss of myelin, axons and oligodendroglial cells, mild reactive gliosis, and sparsely distributed macrophages as well as stenosis resulting from hyaline fibrosis of arterioles and smaller vessels [2], although WMH have also been thought to be due to Wallerian degeneration [27]. In contrast to WMH, subcortical lacunes, which appear as dark foci on T1-weighted MRI and bright foci on T2-weighted MRI in the subcortical nuclei and WM, are complete infarcts where brain tissue is destroyed [16]. The disruption of subcortical-cortical connections by these subcortical vascular lesions may be detrimental to cortical gray matter (CGM) integrity and may result in cognitive impairment. In contrast, the entorhinal cortex (ERC) and hippocampus, sites of early AD pathology [12,13,20,23,24,38], may be less vulnerable to vascular disease because these structures have fewer direct connections to subcortical regions [1]. Thus, the first goal of this study was to investigate the relationship between subcortical vascular disease (i.e., WMH and subcortical lacunes), and CGM, ERC and hippocampal atrophy.

Previous studies have shown that subcortical vascular disease is related to cognitive impairment. Moreover, subjects with subcortical vascular disease are at increased risk for developing dementia [6–8,11,18,25,28,35,36,39]. Clinicopathological studies have found that, for any level of cognitive deficit, the density of neuritic plaques and neurofibrillary tangles in the neocortex is significantly lower in cases of AD mixed with cerebrovascular disease than in cases of AD without cerebrovascular disease [32,35,40], suggesting that cerebrovascular disease has effects in addition to AD pathology on cognition. Furthermore, Esiri et al. found that vascular disease had a greater impact on cognitive performance at early stages of AD than at more advanced AD stages [14]. This finding may suggest that the effects of cerebrovascular disease and AD on cognition are not simply additive, but involve an interaction between the two pathologies. Therefore, the second goal of this study was to test if there is a positive interaction between cerebrovascular disease and AD on CGM, ERC and hippocampal atrophy.

2. Methods

2.1. Subjects

Data from 63 patients (age range: 62–91 years old) with clinical diagnoses of AD and mixed AD/vascular dementia and 77 CN subjects (age range: 63–87 years old) were

included in the analysis, as summarized in Table 1. Fifty patients were diagnosed with AD according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria [29]. Both probable and possible AD patients were included. Another 13 patients were diagnosed as mixed dementia according to the criteria of the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) [5]. Mixed dementia was diagnosed when a patient had symptoms primarily related to vascular dementia and AD was thought to be casually related with dementia. Patients were recruited from the Memory and Aging Center at the University of California, San Francisco (UCSF) and the Alzheimer Center at the University of California, Davis (UCD). CN subjects were recruited from the community. All subjects received a standard battery of neuropsychological tests, as described earlier [30]. CN subjects had cognitive test scores within the normal range. AD and mixed dementia patients were matched for cognitive impairment, assessed by the Mini-Mental State Examination (MMSE) [17]. However, patients with mixed dementia were older than CN subjects and AD patients. Fifteen of the 77 CN subjects, 11 of the 50 AD patients and all 13 mixed dementia patients had subcortical lacunes on MRI. No subject had cortical infarcts. All subjects or their guardians gave written informed consent, approved by the Committees of Human Research at the University of California, San Francisco and Davis.

2.2. Volume measurement

All MRI data were obtained from a 1.5-T Siemens Vision™ System (Siemens Inc., Iselin, NJ). Structural MRI were acquired using a double spin echo sequence (DSE) with TR/TE1/TE2 = 2500/20/80 ms timing, 1.00 mm × 1.25 mm in-plane resolution and approximately 50 contiguous 3 mm thick axial slices oriented along the optic nerve as seen from a midsection sagittal scout MR image. In addition, a volumetric magnetization-prepared rapid gradient echo (MPRAGE) sequence was acquired with TR/TE/TI = 10/7/300 ms timing, 15° flip angle, 1.00 mm × 1.00 mm in-plane resolution, and 1.40 mm thick coronal partitions and oriented orthogonal to the image planes of DSE.

An experienced operator (A.D.) performed manual editing of the ERC and the hippocampus using volumetric T1-weighted images. ERC boundaries were defined using the protocol described by Insausti et al. [19]. Hippocampal boundaries were defined using the protocol described by Watson et al. [37]. To assess global cerebral volume change,

Table 1
Demographics

	CN	AD	Mixed dementia
N (F/M)	77 (40/37)	50 (22/28)	13 (2/11)
N with lacunes (F/M)	15 (6/9)	11 (6/5)	13 (2/11)
Age (years)	75.4 ± 5.4	76.3 ± 5.9	79.9 ± 6.4[a]
Education (years)	15.5 ± 2.8	14.7 ± 3.1	12.6 ± 2.8[a,b]
Duration of symptom (years)	n.a.	4.1 ± 2.8	4.2 ± 5.5
MMSE	29.1 ± 0.9	19.7 ± 6.1*	20.8 ± 4.1[a]

Data represented as mean ± standard deviation. [a]$P < 0.01$ between mixed dementia and CN. [b]$P < 0.05$ between mixed dementia and AD.

 * $P < 0.01$ between AD and CN.

tissue segmentation analysis of the MRI data was performed using software developed in-house [3]. Proton density- and T2-weighted images from DSE and T1-weighted images were used together for tissue segmentation. First-pass segmentation of MRI data into gray matter (GM), WM and CSF was achieved automatically with *k*-means cluster analysis methods. Second-pass, operator-assisted segmentation further classified GM into CGM and subcortical GM, WM into normal WM and WMH, and CSF into sulcal and ventricular CSF. WMH were defined as regions that are hyperintense on proton density- and T2-weighted images and are anatomically located in WM region. WMH are usually not apparent or appear isointense to GM on T1-weighted images. Finally, lacunes were manually outlined on MRI data. Lacunes generally occur in the basal ganglia, capsular and thalamic regions, and appear as hyperintense foci on T2-weighted images, ranging from 3 to 15 mm in diameter. Lacunes are usually hypointense on T1-weighted image and can be either hyperintense or isointense to CSF on proton density-weighted images depending on whether they are cavitated. When lacunes appeared in WM, although this is rare, they were differentiated from WMH by an isointense signal to CSF and lesion size ranging from 3 to 15 mm. Fig. 1 depicts WMH and lacunes on T1-, proton density- and T2-weighted MRI data.

2.3. Statistics

All volumes were normalized to total intracranial volume (TIV) according to: $VOL^n = VOL^r \times TIV^m / TIV^r$, to account for variable head sizes. Here VOL^n and VOL^r are the normalized volume and the raw volume of a subject, respectively, and TIV^m and TIV^r are the mean TIV from all subjects and the TIV of the subject, respectively. The relationship between subcortical vascular disease and CGM, ERC and hippocampus volumes was tested by a multivariate linear regression model. In the model, independent variables were WMH volumes, presence or absence of lacunes, group, age and sex. Dependent variable was CGM, ERC or hippocampal volume. Because the distribution of WMH data was skewed towards more patients having small lesions while fewer subjects presenting large lesions, regressions were also performed with log transformation of WMH data to approximate a normal distribution. The interaction between subcortical vascular
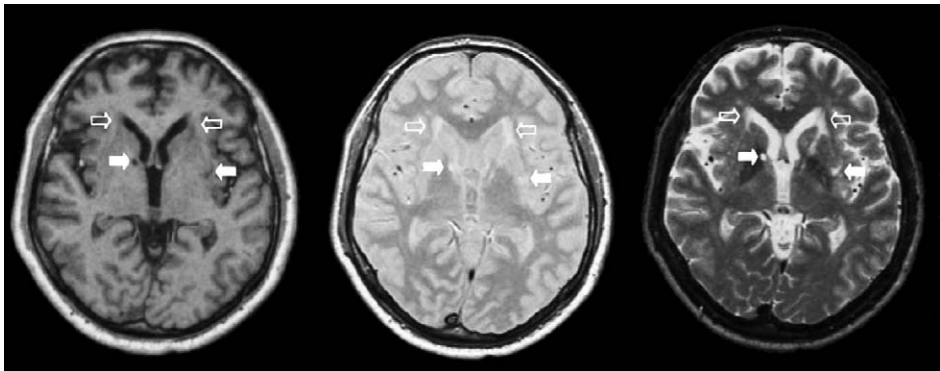

Fig. 1. White matter hyperintensities (empty arrow) and lacunes (solid arrow) on T1-, proton density- and T2-weighted MRI images.

disease and AD on brain atrophy was also tested in the same multivariate linear regression by examining the different relationships between CGM, ERC or hippocampal volume and subcortical vascular disease in CN, AD and mixed dementia. To further investigate whether subcortical vascular disease was more associated with CGM atrophy than ERC and hippocampal atrophy, the volumes of CGM, ERC and hippocampus from all patients were converted into Z-scores and analyzed using a multivariate linear model and post-hoc analyses. Z-scores were calculated according to $(VOL^i - VOL^M)/S.D.$, where VOL^i is measured volume of CGM, ERC or hippocampus from an individual subject, and VOL^M and S.D. are the mean and standard deviation of CGM, ERC or hippocampal volume of CN subjects. Significance was set at $P < 0.05$.

3. Results

3.1. Relationship between CGM volume and subcortical vascular disease (WMH volume and presence of lacunes) in CN, AD and mixed dementia

Fig. 2 depicts the relationship between CGM and WMH volumes in CN, AD and mixed dementia patients. When all three groups were analyzed together, CGM volume was inversely related to WMH volume ($\beta = -0.7$, $F(1,133) = 25.1$, $P < 0.001$, where β is the slope of the regression). The relationship remained significant with log-transformed WMH volumes ($\beta = -8.9$, $F(1,133) = 12.5$, $P < 0.001$). CGM volume was also significantly related to group [$F(2,133) = 34.3$, $P < 0.001$], age [$F(1,133) = 26.7$, $P < 0.001$] and sex [$F(1,133) = 16.0$, $P < 0.001$]. However, there was no significant relationship between CGM volume and presence of lacunes [$F(1,133) = 0.1$, $P > 0.7$]. Further, there was no interaction between group and WMH volume [$F(1,133) = 0.2$, $P > 0.7$], implying that effects of AD pathology and WMH on CGM loss may be additive. However, our inability to detect an interaction between groups may have been due to lack of statistical power. Power calculation showed that with the current sample size, power to detect a 50% positive interaction ($P = 0.05$) between group and WMH volume on CGM volume was only 37%. Because the frequency of lacunes was different between groups ($\chi^2 = 5.1$,
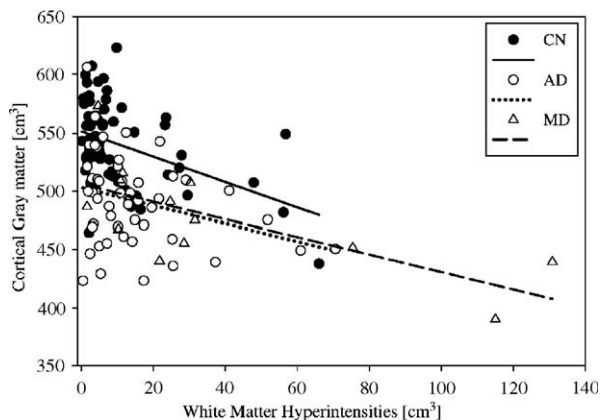

Fig. 2. Relationship between volumes of cortical gray matter and white matter hyperintensities in cognitively normal controls (CN), patients with Alzheimer's diseases (AD) and mixed dementia (MD).
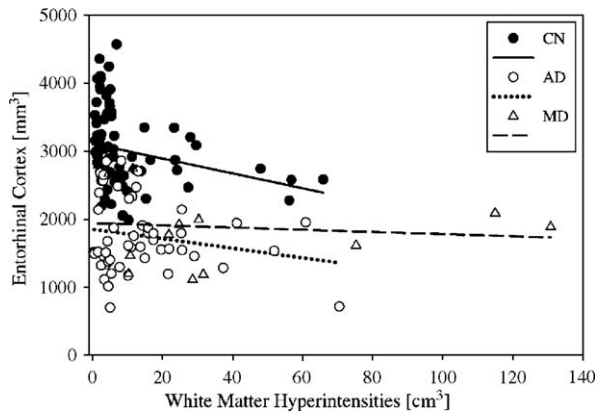
Fig. 3. Relationship between volumes of entorhinal cortex and white matter hyperintensities in cognitively normal controls (CN), patients with Alzheimer's diseases (AD) and mixed dementia (MD).

$P < 0.05$), including group as a factor in the model could introduce a spurious relationship between CGM volume and presence of lacunes. For this reason, we repeated the analysis without group as a factor in the model. This analysis also did not reveal a significant relationship between CGM volume and presence of lacunes [$F(1,135) = 0.01$, $P > 0.9$], implying that lack of a relationship between CGM atrophy and presence of lacunes in the original analysis is not due to an effect of group in the model.

3.2. Relationship between ERC volume and subcortical vascular disease (WMH volume and presence of lacunes) in CN, AD and mixed dementia

Fig. 3 depicts the relationship between ERC and WMH volumes in CN, AD and mixed dementia patients. In contrast to CGM, ERC volume was not related to WMH volume [$F(1,133) = 2.8$, $P = 0.1$] when all three groups were analyzed together, although this became a trend [$F(1,133) = 3.9$, $P = 0.051$] for log-transformed WMH volumes. There was also no relationship between ERC volume and presence of lacunes [$F(1,133) = 0.4$, $P > 0.5$], age [$F(1,133) = 0.5$, $P > 0.4$] and sex [$F(1,133) = 2.0$, $P > 0.1$].

However, ERC volume was significantly related to group [$F(2,133) = 66.7$, $P < 0.001$]. Similar to CGM, removing group as a factor from the model also did not yield a significant relationship between ERC volume and presence of lacunes [$F(1,135) = 0.7$, $P > 0.3$], implying that lack of a significant relationship between ERC atrophy and presence of lacunes is not due to an effect of group in the original model.

3.3. Relationship between hippocampal volume and subcortical vascular disease (WMH volume and presence of lacunes) in CN, AD and mixed dementia

Fig. 4 depicts the relationship between hippocampal and WMH volumes in CN, AD and mixed dementia patients. Similar to the ERC, there was no relationship between hippocampal volume and WMH volume [$F(1,133) = 0.07$, $P > 0.7$] or presence of lacunes [$F(1,133) = 0.1$, $P > 0.7$]. The relationship remained nonsignificant with log-transformed WMH volumes [$F(1,133) = 0.07$, $P > 0.7$]. However, hippocampal volume was significantly related to group [$F(2,133) = 59.9$, $P < 0.001$], age [$F(1,133) = 6.8$, $P < 0.02$] and sex
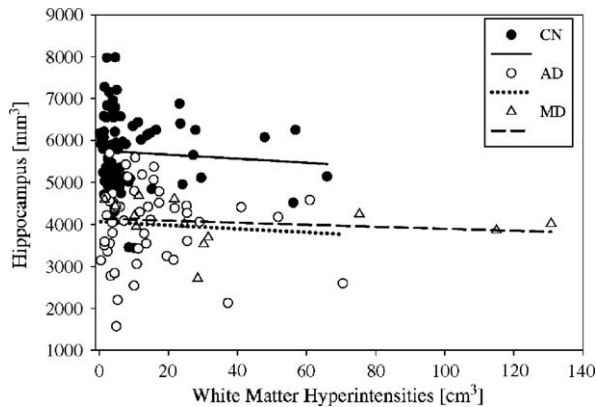
Fig. 4. Relationship between volumes of hippocampus and white matter hyperintensities in cognitively normal controls (CN), patients with Alzheimer's diseases (AD) and mixed dementia (MD).

$[F(1,133)=4.7, P<0.05]$. Similar to CGM, removing group as a factor from the model also did not yield a significant relationship between hippocampal volume and presence of lacunes $[F(1,135)=0.7, P>0.4]$, implying that lack of a significant relationship between hippocampal atrophy and presence of lacunes is not due to an effect of group in the original model.

3.4. Different relationship between WMH volume and CGM, ERC and hippocampal volumes

The relationships between CGM, ERC and hippocampal volume Z-scores with WMH volume were significantly different $[F(2,179)=4.5, P<0.02]$ after taking into account effects of group, presence or absence of lacunes, age and sex. Using log-transformed WMH data yielded a trend of different relationships $[F(2,179)=2.5, P=0.08]$ between CGM, ERC and hippocampal volume Z-scores with WMH volume. Post-hoc analyses revealed a stronger relationship between WMH volume and CGM volume Z-score than between WMH volume and ERC volume Z-score $[F(1,118)=5.5, P<0.03]$ or hippocampal volume Z-score $[F(1,118)=5.4, P<0.03]$. Repeating this analysis with log-transformed WMH data resulted in a trend for a stronger relationship between WMH volume and CGM volume Z-score than between WMH volume and ERC volume Z-score $[F(1,118)=3.5, P=0.06]$, while the relationship between WMH volume and CGM volume Z-score remained stronger than the relationship between WMH volume and hippocampal volume Z-score $[F(1,118)=6.7, P=0.01]$. This suggests that WMH have a greater effect on CGM volume loss than on ERC and the hippocampal volume loss. However, the relationship between WMH volume and ERC volume Z-scores did not differ significantly from that between WMH volume and hippocampal volume Z-scores whether WMH volumes were log-transformed or not (both $P>0.4$). Fig. 5 depicts the volumes of CGM, ERC and hippocampus (all expressed in Z-scores relative to controls) as function of WMH volume in demented patients. AD and mixed dementia patients were combined to demonstrate the overall effect of WMH on brain atrophy, independent of the type of dementia. The intercepts of the regressions represent the extent of atrophy of CGM, ERC
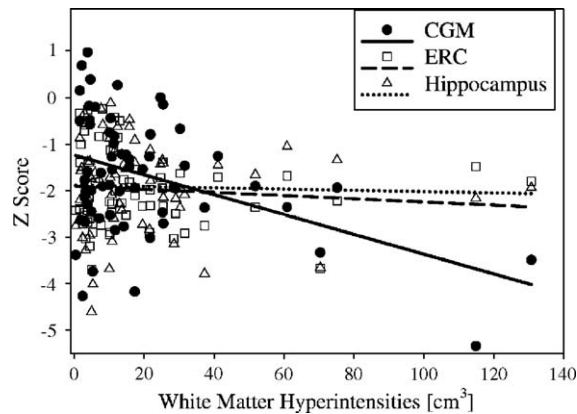
Fig. 5. Volumes of cortical gray matter (CGM), entorhinal cortex (ERC) and hippocampus (all expressed in *Z*-scores relative to controls) as function of WMH volume in demented patients; AD and mixed dementia are combined to demonstrate the overall effect of WMH on brain atrophy, independent of the type of dementia.

or hippocampus due to AD, while the slopes represent the extend of atrophy of CGM, ERC or hippocampus due to subcortical vascular disease, assessed as WMH volumes. Therefore, the figure shows that AD had a smaller effect (i.e., a smaller intercept) on CGM volume than on ERC and hippocampal volume. In contrast, WMH volume had a larger effect (i.e., a steeper slope) on CGM volume than ERC and hippocampal volumes.

4. Discussion

The major findings of this study were: (1) CGM volume was inversely related to WMH volume while ERC and hippocampal volumes were not; (2) there was no significant relationship between the presence of subcortical lacunes and CGM, ERC and hippocampal volumes.

The first finding of this study was that, in CN, AD and mixed dementia patients, CGM volume was inversely related to WMH volume while ERC and hippocampal volumes were not. This result supports our initial assumption that the ERC and hippocampus may be less vulnerable to vascular disease than the cortex because these structures have fewer direct connections to subcortical regions. There are at least two possible explanations for the current finding. The first explanation is that WMH represents generalized ischemic damage and that the cortex is more vulnerable to such damage, while the ERC and hippocampus are less vulnerable. However, previous animal studies showed that the hippocampus is especially vulnerable to hypoxia and ischemic insults [4,33]. Therefore, if WMH represents generalized cerebrovascular disease causing generalized ischemic neuronal damage, one would expect a relationship between increased WMH volumes and decreased hippocampal volumes. Therefore, our finding of no significant relationship between WMH, ERC and hippocampal volumes suggests that the primary mechanism of cortical neurodegeneration in subcortical ischemic vascular disease may be deafferentation of cortical–subcortical connections, rather than generalized ischemic damage. Another explanation is that WMH may represent Wallerian degenerations of axons, connected to cortical neurons. This would also explain lack of the relationship of WMH with ERC and

hippocampal volumes, because there are fewer direct axonal connections to ERC and hippocampus than to cortical regions [1]. Using log-transformed data revealed a trend of significant relationship between WMH and ERC atrophy, but no relationship between WMH and hippocampal atrophy. A possible explanation could be that the ERC is more directly connected to subcortical regions than the hippocampus, because ERC is part of the cortex, which was strongly affected by WMH. More studies are needed to further investigate the differential effect of WMH on ERC and hippocampal atrophy. However, whether WMH in AD are caused by Wallerian degeneration remains controversial [2,27]. Furthermore, Wallerian degeneration cannot fully explain WMH in CN subjects, because cortical atrophy was substantially less in CN than in AD, although both groups presented similar amounts of WMH. In addition, the lack of correlation between the stage of the disease (Braak I–VI) and the aberrations of cerebral microvessels also suggest that WMH should not be the consequence of AD [9].

The second finding of this study was that there were no significant relationships between the presence of subcortical lacunes and CGM, ERC and hippocampal atrophy in the patients with AD and mixed dementia, despite strong relationships of regional atrophy with WMH. This is consistent with a previous report from this group that found no relationship between subcortical lacunes and CGM and hippocampal volume loss using Spearman's rank correlation analyses without accounting for other confounds [15]. There are several reasons why the presence of subcortical lacunes were not related to CGM, ERC and hippocampal atrophy in the patients with AD and mixed dementia: (1) if brain atrophy in AD and mixed dementia patients is dominated by AD pathology, it may be difficult to detect the additional effects of subcortical lacunes; (2) a previous study reported that the severity of dementia in AD patients was not significantly affected by concomitant small (<10 cm^3) infarcts [26]. In the current study, most patients had small (<1 cm^3) subcortical lacunes. Thus, it is possible that concomitant small subcortical lacunes also does not contribute significantly to brain atrophy in AD patients; (3) a previous neuropathological study found no correlation between the severity of amyloid angiopathy and subcortical lacunes [22]. Therefore, it is possible that the presence of subcortical lacunes does not correlate with the severity of cerebral ischemia throughout the brain.

It is interesting to note that, in the same group of subjects, CGM volume was related to WMH volume but not to the presence of subcortical lacunes. This may relate to the fact that WMH and subcortical lacunes represent brain damage in different subcortical regions. WMH are lesions in the WM area. Although lacunes may also appear in the WM area, most occur in the subcortical nuclei [36]. In addition, WMH typically involves larger subcortical areas than subcortical lacunes. Thus, WMH and subcortical lacunes may differentially impact cortical–subcortical connections and this may explain why CGM loss had different relationships to WMH and subcortical lacunes. On the other hand, if WMH and subcortical lacunes both represent generalized cerebrovascular disease that causes secondary gross neuronal damage, one would expect CGM volume to have a similar relationship with WMH and subcortical lacunes. The fact that we did not detect similar relationships between CGM loss and WMH and subcortical lacunes further supports the notion that the primary mechanism of cortical neurodegeneration in subcortical ischemic vascular disease is the deafferentation of cortical–subcortical connections.

Out of our expectation, a positive interaction between WMH volume and diagnosis on CGM loss was not detected in this study. This suggests that effects of AD pathology and WMH on cortical atrophy may be additive. However, we have to be aware that no interaction between AD pathology and WMH on cortical atrophy may be due to limited power in this study. In addition, one previous study found that cerebrovascular disease had a greater capacity to influence cognitive impairment during the early stage of AD rather than during more advanced stage of the disease [14]. Thus, the interaction between subcortical vascular disease and AD on brain atrophy may also be different during different stages of AD. Due to the fact that the patients in this study were moderate demented, further studies are needed to elucidate how these two pathologies interact with each other on brain atrophy and the development of dementia.

Because presence of WMH can skew intensity distributions for tissue segmentation, misclassifications of gray and white matter may have occurred in this study with segmentation based on k-means cluster analysis. For this reason, we performed additional analyses to examine the extent to which tissue misclassification may have affected the relationship between CGM and WMH volume. Sixty-four subjects from the present population who had a representative distribution of WMH volume were selected for re-segmented. Cluster analyses of GM, WM and CSF in these 64 subjects were performed after WMH had been identified and removed from the MRI data. Results revealed similar relationships between CGM and WMH regardless of the segmentation method used (unpublished data). Thus, it is unlikely that the relationship between CGM and WMH volume was impacted by tissue misclassification during segmentation.

This study has several limitations. Previous spectroscopic and PET studies have shown that patients with vascular dementia have hypometabolism and hypoperfusion predominately in frontal and parietal lobes [31,34]. Therefore, it is possible that WMH may differentially affect atrophy in different regions of the brain. However, we were unable to determine the impact of WMH on different brain regions because we only calculated gray matter volume for the entire brain. Another limitation of this study is that we did not have pathological confirmation of presence of subcortical lacunes. Because subcortical lacunes were identified solely from MRI images, we do not know whether the subcortical lacunes represent complete infarct, incomplete infarct, gliosis or paravascular space. Thus it is possible that we did not detect a relationship between subcortical lacunes and brain atrophy because some of the subcortical lacunes had been misclassified. Despite these limitations, our results indicate that WMH have a greater effect on the cortex than the ERC or hippocampus and that WMH's effect on the cortex may be independent of AD in demented patients with AD and subcortical vascular disease pathologies.

Acknowledgments

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